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VALIDATION OF A MODIFIED ONE-STEP REBREATHING TECHNIQUE FOR NON-INVASIVE MEASUREMENT OF SUBMAXIMAL CARDIAC OUTPUT

U S ARMY RESEARCH INSTITUTE
OF
ENVIRONMENTAL MEDICINE
Natick, Massachusetts

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The primary objectives of this study were to modify the Farhi one-step carbon dioxide (CO_2) rebreathing technique for measuring cardiac output during rest and submaximal exercise, and then to validate our modifications. The novelty of Farhi's technique is that it 1) requires only one-step to acquire all data necessary for computations, 2) is noninvasive, 3) takes less than 30 seconds for each rebreathing maneuver, 4) can be repeated at rapid intervals (1-2 minutes), and 5) is accurate and highly reproducible. Because a low flow rate analyzer (mass spectrometer) that Farhi specified as being essential for monitoring CO_2 at the mouth during rebreathing was available to us only on a limited basis and is not readily field portable, we modified both available equipment and technique. By substituting a high flow rate analyzer (Beckman LB-2 CO_2 analyzer) for the mass spectrometer, reducing the length of sampling

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tubing to the analyzer and adding a recirculation circuit from the exhaust outlet of the analyzer to an inlet at the base of the rebreathing bag, we were able to recirculate the subject's expired gas and achieve no loss of rebreathing bag volume. No statistically significant differences in estimate of cardiac output were noted between the mass spectrometer and LB-2 analyzer with recirculation circuit during rest or submaximal exercise (cycling). Heart rate and oxygen uptake were highly correlated with cardiac output and agreed well with the literature, irrespective of the CO_2 analyzer system used. One factor critical to the accuracy of the CO_2 measured at the mouth and to the calculation of cardiac output is the initial rebreathing bag volume. A unique feature of our method is that the subject's tidal volume is measured prior to the maneuver and then used as the initial rebreathing bag volume. Varying the bag volume by $\pm$ 0.2L from the tidal volume had no significant effect on the estimate of cardiac output during rest or exercise. Using tidal volume as the bag volume and rebreathing frequencies of 27-36 min^{-1} during rest and 30-45 min^{-1} during exercise, we obtained results that were highly reproducible on a daily basis. Because our modifications were successful, quick, reliable and noninvasive measurements of cardiac output (and stroke volume) are feasible in heat injured and dehydrated troops not only in the laboratory but also in the field.

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VALIDATION OF A MODIFIED ONE-STEP REBREATHING TECHNIQUE FOR NONINVASIVE MEASUREMENT OF SUBMAXIMAL CARDIAC OUTPUT

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ABSTRACT

The primary objectives of this study were to modify the Farhi one-step carbon dioxide (CO_2) rebreathing technique for measuring cardiac output during rest and submaximal exercise, and then to validate our modifications. The novelty of Farhi's technique is that it 1) requires only one-step to acquire all data necessary for computations, 2) is noninvasive, 3) takes less than 30 seconds for each rebreathing maneuver, 4) can be repeated at rapid intervals (1-2 minutes), and 5) is accurate and highly reproducible. Because a low flow rate analyzer (mass spectrometer) that Farhi specified as being essential for monitoring CO_2 at the mouth during rebreathing was available to us only on a limited basis and is not readily field portable, we modified both available equipment and technique. By substituting a high flow rate analyzer (Beckman LB-2 CO_2 analyzer) for the mass spectrometer, reducing the length of sampling tubing to the analyzer and adding a recirculation circuit from the exhaust outlet of the analyzer to an inlet at the base of the rebreathing bag, we were able to recirculate the subject's expired gas and achieve no loss of rebreathing bag volume. No statistically significant differences in estimate of cardiac output were noted between the mass spectrometer and LB-2 analyzer with recirculation circuit during rest or submaximal exercise (cycling). Heart rate and oxygen uptake were highly correlated with cardiac output and agreed well with the literature, irrespective of the CO_2 analyzer system used. One factor critical to the accuracy of the CO_2 measured at the mouth and to the calculation of cardiac output is the initial rebreathing bag volume. A unique feature of our method is that the subject's tidal volume is measured prior to the maneuver and then used as the initial rebreathing bag volume. Varying the bag volume by $\pm$ 0.2L from the tidal volume had no significant

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INTRODUCTION

Thermoregulatory adaptations to work in a hot environment place increased demands on the circulatory system which, in humans, are met by increasing cardiac output and shifting peripheral blood flow (12). An impaired circulatory function is hypothesized to contribute to inefficient temperature regulation in hypohydration (9, 13) and in heat intolerance in former heatstroke patients (14). Studies in our laboratory with former heatstroke patients created a requirement for a measure of cardiac output in humans exercising in the heat.

Several different approaches for determining cardiac output in humans are available. The Fick method is the standard for measuring cardiac output in both animal and human subjects. Although a direct measure of the output of the heart, the Fick technique is invasive requiring catheterization and is, therefore, not without risk and not always justifiable. Two other invasive techniques which have limited application in human research in a laboratory setting are thermo- and dye dilution (1, 3). To circumvent unnecessary subject risk, noninvasive approaches requiring the subject to rebreathe a gas such as acetylene or carbon dioxide (CO_2) have been developed (1, 3, 5, 8, 15). For most of these CO_2 rebreathing methods, several sequential steps taking up to 10 minutes are required to measure all of the data necessary to solve the Fick equation for CO_2. The form used for this relationship is $\dot{Q} = \dot{V}CO_2/(C\bar{v}CO_2 - CcCO_2)$ where $\dot{Q}$= pulmonary blood flow. The CO_2 output ($\dot{V}CO_2$) is measured from a 5 minute expired air collection. End-tidal CO_2 which is also monitored during this 5 minutes, is used as an index of the CO_2 at the end of the pulmonary capillaries (denoted by $CcCO_2$ in this equation). The CO_2 concentration in mixed venous blood ($C\bar{v}CO_2$) is continuously measured during the rebreathing.

The "one step" rebreathing technique devised by Farhi and coworkers (1) is best suited for our research investigation. The uniqueness of Farhi's method is that all of the information required to solve the Fick equation is obtained in one simple step eliminating the need to collect, measure and analyze expired gases. Several other reasons for favoring this technique over the others are that it 1) requires analysis of only one gas, 2) is user friendly in that it takes less than 30 seconds per maneuver, 3) can be repeated at 1-2 minute intervals, and 4) is accurate to ± 0.5 $L*min^{-1}$. Briefly, an individual rebreathes a known volume of air at an increased tidal volume and breathing frequency which are chosen so as to increase alveolar ventilation, and produce a fall in alveolar PCO_2. During subsequent breaths, the increase in alveolar PCO_2 is continuously monitored at the mouth. The modified Fick equation for CO_2 used to determine pulmonary blood flow ($\dot{Q}$) with the Farhi technique is $\dot{Q} = (\Delta \dot{V}CO_2/T)/(C\bar{v}CO_2 - C\bar{c}CO_2)$. The $\Delta \dot{V}CO_2$ is calculated from the increase in PCO_2 in the bag-lung system and is equivalent to the cumulative loss of CO_2 from the pulmonary circulation. End capillary PCO_2 ($C\bar{c}CO_2$) is obtained from the mean alveolar PCO_2 during time T, and mixed venous CO_2 is derived from a calculated equilibrium CO_2. A complete derivation of the mathematical formulas can be gotten from Farhi's article (1).

Farhi et al. (1) stressed that although their technique for estimating cardiac output appears relatively simple, the investigator must exercise caution to avoid violating any of the assumptions upon which the calculations are based. The reader is referred to Farhi's article (1) for a complete description of assumptions. Of critical importance to Farhi's technique is the rebreathing bag volume which should remain constant throughout the rebreathing maneuver. Because $\Delta \dot{V}CO_2$ is calculated from the CO_2 accumulation in the bag-lung system and is both a volume and time dependent measure, the

accuracy of its determination depends on a constant bag volume. To avoid significant loss of bag volume during the maneuver, Farhi recommended using a low flow rate analyzer or mass spectrometer with a sampling rate of 40-60 $ml*min^{-1}$ for measuring the subject's carbon dioxide (CO_2) equilibration. A standard CO_2 analyzer such as the Beckman or Sensormedics with sampling rates of 500 $ml*min^{-1}$ was not recommended because it draws off more than eight times the sample of a mass spectrometer.

The purpose of this report is 1) to describe the recirculation circuit which was configured for using the Farhi et al. (1) one-step rebreathing technique with a high flow rate analyzer (Beckman LB-2 CO_2 analyzer) and 2) to provide validation of this recirculation circuit for measuring cardiac output during rest and exercise. Because a low flow rate analyzer was not available for our continuous use before the scheduled arrival of our subjects, we attempted and successfully succeeded in generating CO_2 equilibration curves with a Beckman LB-2 CO_2 analyzer (model 240). No net loss of bag volume was achieved by recirculating the subject's expired gases, after being analyzed by the LB-2 CO_2 analyzer, back to the rebreathing bag.

APPARATUS DESCRIPTION

The components necessary for the rebreathing technique consist of a 1.5L Collins calibration syringe (20 ml gradations), 5L anesthesia bag, T-shaped Collins stopcock valve (deadspace= 14 ml), Beckman LB-2 Carbon Dioxide (CO_2) analyzer, Hewlett Packard x-y plotter (model 7004B), Altek (ACT23-1-RP1) digitizing table and controller (AC40-4888-DKF), and Hewlett Packard micro-computer (HP 9000 series 300). The apparatus configuration during a breathing maneuver is shown in FIGURE 1.

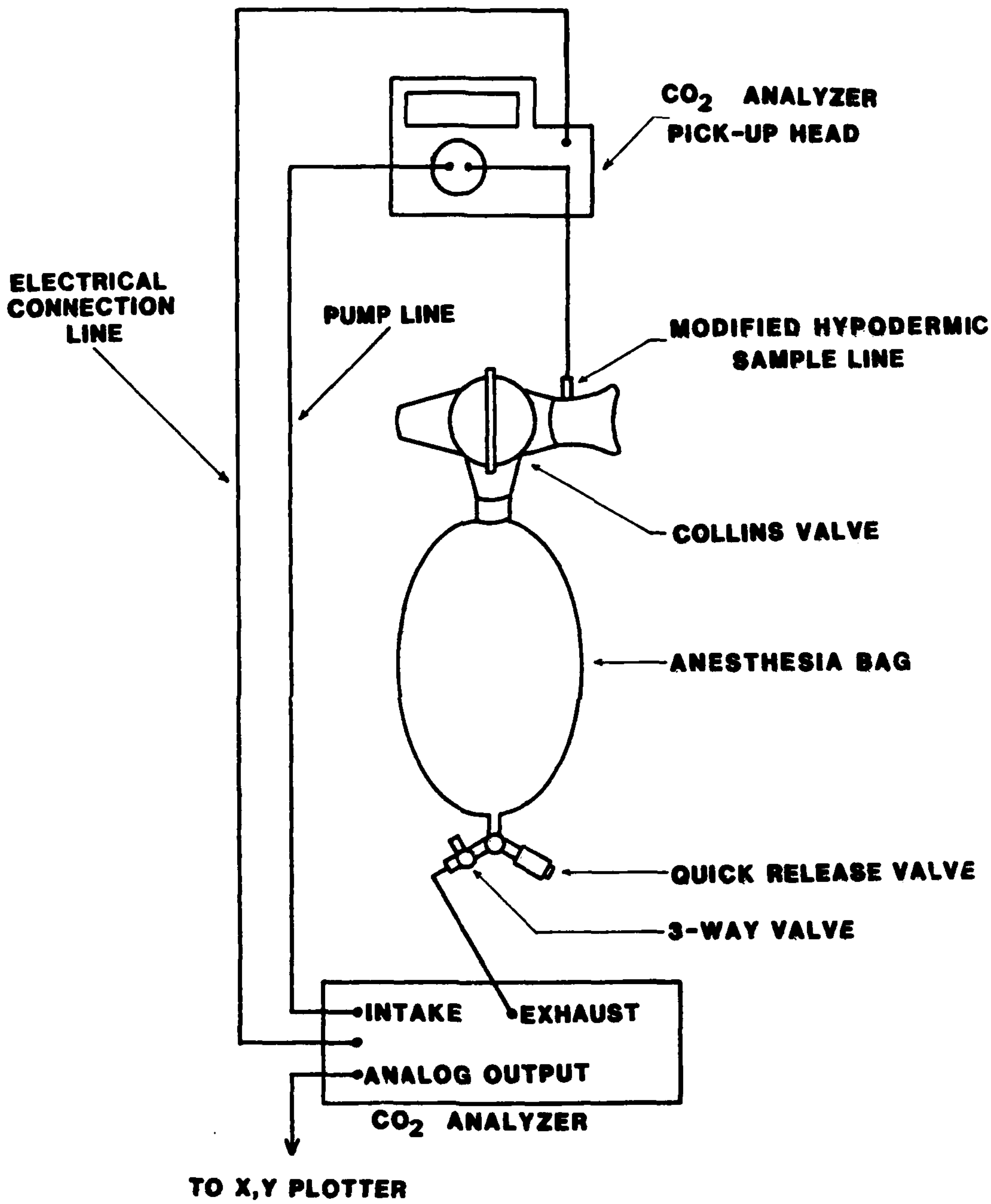

FIGURE 1 Apparatus configuration

A modified 15 gauge stainless steel hypodermic needle permanently affixed to the common port of the T-shaped Collins valve served as the sampling inlet of the LB-2 CO_2 analyzer. A mouthpiece (Vacumed, large adult with bite-block) was also attached to one of the remaining ports. A "V" shaped aluminum bar was inserted into the apex of the bag to assist in gas mixing and to prevent premature collapse of the bag. To prevent loss of bag volume, analyzed gas was returned to the rebreathing anesthesia bag via a recirculation circuit.

This recirculation circuit interposed between the LB-2 CO_2 analyzer and the anesthesia bag consisted of the following: a small Y-tube (Kartell, 4 mm diameter) was mounted into the nipple at the base of the anesthesia bag. The other two openings of this tube were connected to a 3-way stopcock (Nalgene Labware, 4 mm diameter) and to a one-way quick connect fitting (Swagelock). During the rebreathing maneuver, this 3-way stopcock was connected to a 1.2 m (0.7 m if subject is sedentary) length of Tygon tubing (ID 3/16", OD 5/16") which is connected to the exhaust port of the LB-2 CO_2 analyzer. To optimize recirculation time, the length of the tubing extending from the sampling inlet on the CO_2 sensor head to the analyzer pump was reduced from 4.6 m to 1.7 m. The total length of all sampling and recirculating tubing was 2.1 m during rest and 2.9 m during exercise.

REBREATHING MANEUVER

Prior to each rebreathing maneuver, an average tidal volume (V_T) was measured with a Pneumoscan spirometer (model S-300C). A 1.5L calibrating syringe was used to dispense the subject's V_T, into previously evacuated 5L anesthesia bags. For resting measures the bags were filled with room air, and during exercise, a 60% oxygen/40% nitrogen gas mixture was used to assure complete oxygenation of mixed venous blood during the rebreathing maneuver.

The subject donned a noseclip and breathed room air through the mouthpiece attached to the stopcock/bag assembly before and between measures. The rebreathing maneuver consisted of the subject turning the stopcock at the end of a normal expiration and then rebreathing at a frequency of 25-35 breaths*min^{-1} at rest and 30-45 breaths*min^{-1} during exercise for approximately 20 sec, maximally inhaling and exhaling the bag volume. To engage the recirculation circuit, the small secondary 3-way stopcock mounted at the base of the anesthesia bag was turned by the investigator during the first breath of the rebreathing maneuver.

Tracings of mouth CO_2 concentration during rebreathing were recorded on the x-y plotter connected to the analog output of the LB-2 CO_2 analyzer. The tracings were digitized and cardiac output (Q) was computed using a microcomputer. The BASIC language program used for analysis of the tracings is based on the theory and assumptions proposed by Farhi et al. (1). Essentially, the program utilizes a modified Fick equation for CO_2 to determine pulmonary blood flow, which is equivalent to cardiac output under most circumstances. This equation was described in the Introduction section.

SYSTEM EVALUATION

Six physically fit and active subjects (5 males; 1 female) participated under written informed consent. Physical characteristics are shown for the individuals in TABLE 1. The means $\pm$ 1SE are age= 32$\pm$ 3 yr; weight= 75.9$\pm$ 6.5 kg; height= 181$\pm$ 4cm. Maximal oxygen consumption ($\dot{V}O_2$max) was assessed while the subjects performed exhaustive graded exercise on a Collins Pedalmate cycle ergometer (average $\dot{V}O_2$max= 3.74$\pm$ 0.29 L*min^{-1}). During the max test and all subsequent trials, expired gases were collected and measured using a semi-automated system consisting of gasometer (Parkinson-Cowan), and carbon dioxide

TABLE 1

SUBJECT CHARACTERISTICS

Subject	Sex	Age (yr)	Height (cm)	Weight (kg)	$\dot{V}O_2max$# ($L*min^{-1}$)	$\dot{V}O_2max$ ($ml*min^{-1}*kg^{-1}$)
1	M	28	183	100.0	3.99	40.97
2	M	35	183	71.2	3.70	52.02
3	M	42	188	87.9	3.89	44.25
4	M	22	180	64.5	4.51	69.92
5	M	30	188	74.2	3.94	53.15
6	F	34	161	57.1	2.38	41.69
mean		32	181	75.9	3.74	50.33
±1SD		7	10	15.8	0.72	10.89
±1SE		3	4	6.5	0.29	4.45

$\dot{V}O_2max$ was obtained on bicycle ergometer.

(Beckman LB-2) and oxygen (Applied Electrochemistry S3A) analyzers interfaced with Hewlett Packard scanner, digital voltmeter and 85B computer.

Following the max test, subjects performed three exercise protocols (day 1, 2 and 3) on non-consecutive days. Exercise consisted of progressively increasing work loads on the bicycle ergometer.

The "day 1" protocol was designed to compare values of cardiac output ($\dot{Q}$) measured with the rebreathing technique using the Beckman LB-2 analyzer (flow rate= 500 ml*min^{-1}) to those obtained with a mass spectrometer (Perkin Elmer model MGA-1100) (flow rate= 40-60 ml*min^{-1}). Six (6) subjects participated in the day 1 protocol. Each subject pedaled at each of four (4) target work loads (25%, 40%, 55%, and 70% of $\dot{V}O_2$max) for fifteen minutes. Steady state oxygen uptake ($\dot{V}O_2$) was measured five minutes into each work load, and was used to confirm the %$\dot{V}O_2$max. During this interval, average tidal volume (V_T) was measured for use as the rebreathing bag volume. During the next 8-12 minutes of bicycling, four (4) estimates of $\dot{Q}$ were obtained with a 2 minute recovery period between measures. The first and the last estimates were obtained from the mass spectrometer and the intermediate measures of $\dot{Q}$ were generated by the Beckman LB-2 CO_2 analyzer. $\dot{V}O_2$ and V_T were again assessed prior to each increase in work load. Heart rate (HR) was measured immediately before and during each rebreathing maneuver using a Hewlett Packard telemetry system.

The "day 2" protocol (n= 4) was designed to investigate the effect of bag volume on the estimate of $\dot{Q}$ obtained with the rebreathing technique using the Beckman LB-2 analyzer and recirculation circuit. The experiment consisted of 4 subjects bicycling for 20 minutes at each of 2 target levels: 35% $\dot{V}O_2$max and 55% $\dot{V}O_2$max. After five minutes of bicycling at each work load, $\dot{V}O_2$ was measured to verify %$\dot{V}O_2$max and V_T was assessed for dispensing bag volume.

Immediately following these measures, three estimates of Q were obtained: one with a bag volume equal to the subjects tidal volume (V_T), and the other two with volumes 0.2L greater than and less than V_T. We chose to vary the bag volume by 0.2L because this volume represents about 10% of the anticipated exercise V_T. This amount of variability was reported by Priban (11) and was recommended by Pendergast (personal communication). $\dot{V}O_2$ and V_T were verified after duplicate measures of $\dot{Q}$. Heart rate was assessed prior to and during each rebreathing maneuver.

"Day 3" protocol (n= 4) was designed to examine the effects of breath frequency during the rebreathing maneuver on the estimate of $\dot{Q}$ using the LB-2 analyzer and recirculation circuit. Cardiac output was determined in each of four (4) sedentary subjects after they had rested in a seated position for at least 20 minutes. Each subject performed duplicate rebreathing maneuvers at each of three (3) target frequencies (30 min^{-1}, 35 min^{-1} and 50 min^{-1}).

Repetitive measures for each of $\dot{Q}$ and $\dot{V}O_2$ were averaged to obtain mean values at each work level for each subject. Cardiac output was plotted as a function of $\dot{V}O_2$ for each analyzer and then combined using linear regression analysis. Comparisons between analyzer systems, bag volumes, and rebreathing frequencies were done using ANOVA. Significance was accepted at 0.05 level. Statistical analyses were performed using BMDP and Picsure statistical packages.

RESULTS OF SYSTEM EVALUATION

The subjects of this study are considered to be physically fit as judged by the bicycle $\dot{V}O_2max$ values (TABLE 1) and active participation in daily exercise regiments. All subjects run at least 3 miles several times weekly. In addition, subjects 1 and 3 participate in weight-lifting, 2, 4 and 5 in distance running, and 6 in bicycling and bodybuilding.

Day 1. Comparison of high flow rate CO_2 analyzer with recirculation circuit and low flow rate mass spectrometer

Heart rate (HR), $\dot{V}O_2$ and $\dot{Q}$ (regardless of CO_2 measuring device) all demonstrated statistically significant ($p < 0.05$) increases with increased work load. These data are shown for individual subjects in TABLE 2. These linear increases in HR and $\dot{V}O_2$ associated with increased work load were highly correlated ($R = 0.93$, $SD = 0.32$, $p < 0.05$) as seen in FIGURE 2. Also, HR and $\dot{V}O_2$ were highly correlated with $\dot{Q}$ irrespective of the CO_2 analyzer system used (FIGURES 3-4, $p < 0.05$).

Representative tracings obtained during the rebreathing maneuver with the two CO_2 analyzers are shown in FIGURE 5. The correlation between $\dot{Q}$ measured with the mass spectrometer and $\dot{Q}$ measured with the LB-2 CO_2 analyzer and recirculation circuit was highly significant (FIGURE 6, $R = 0.97$ $SD = 1.2\ L*min^{-1}$). Cardiac output measured with the LB-2 analyzer was, on average, 0.35 $L*min^{-1}$ less than that measured with the low flow rate CO_2 analyzer, but this difference was statistically insignificant.

Day 2. Comparison of varying bag volumes on cardiac output measured using the LB-2 analyzer and recirculation circuit

Varying the bag volume by $\pm$ 0.2L from the tidal volume (V_T) resulted in no significant differences in estimates of $\dot{Q}$ measured during exercise using our recirculation circuit (TABLE 3). Directional trends in cardiac output were not seen when bag volume was varied by $\pm$ 0.2L from exercise V_T. The relationships between bag volumes of V_T, V_T+ 0.2L, and V_T- 0.2L were all highly correlated ($R = 0.96$, FIGURES 7-9).

Estimates of resting cardiac output are shown for four subjects in TABLE 3. Varying the bag volume by $\pm$ 0.1L represented a change from the measured rest V_T of 6%, 14%, 13%, and 17% in subjects 1, 4, 5, and 6,

TABLE 2

COMPARISON OF VALUES FOR CARDIAC OUTPUT USING

THE HIGH FLOW RATE CO_2 ANALYZER WITH RECIRCULATION CIRCUIT

AND THE LOW FLOW RATE ANALYZER

Subject	Watts	Target $\%\dot{V}O_2max$	Actual $\%\dot{V}O_2max$	$\dot{V}O_2$ ($L*min^{-1}$)	HR (bpm)	$\dot{Q}_{LB-2}$ + ($L*min^{-1}$)	$\dot{Q}_{MS}$ * ($L*min^{-1}$)
1	80	25	28	1.10	86	15.0	13.9
	129	40	41	1.64	100	18.2	17.3
	177	55	63	2.53	130	23.4	22.4
	224	70	82	3.28	165	25.3	24.5
2	74	25	28	1.02	79	10.15	10.1
	119	40	37	1.35	91	12.3	13.6
	164	55	55	2.03	110	15.8	15.5
	200	70	73	2.70	130	21.7	20.2
3	78	25	24	0.92	98	12.8	15.1
	125	40	35	1.36	115	15.9	16.5
	172	55	51	1.99	132	19.8	20.9
	219	70	87	3.39	162	23.8	21.3
4	91	25	21	0.93	85	11.2	11.55
	145	40	30	1.38	111	16.8	15.9
	200	55	56	2.53	148	22.25	20.3
5	78	25	26	1.03	90	9.5	9.3
	127	40	38	1.50	108	11.8	11.1
	175	55	58	2.28	136	16.3	17.9
	222	70	73	2.86	170	19.2	21.25
6	50	25	25	0.59	72	7.3	7.0
	76	40	33	0.79	92	9.3	9.6
	105	55	52	1.23	119	12.9	12.5

+ $\dot{Q}_{LB-2}$= cardiac output obtained with Beckman LB-2 CO_2 analyzer (flow rate= 500 $ml*min^{-1}$) and recirculation circuit

* $\dot{Q}_{MS}$= cardiac output determined using the Perkin Elmer mass spectrometer (low flow rate= 60 $ml*min^{-1}$)

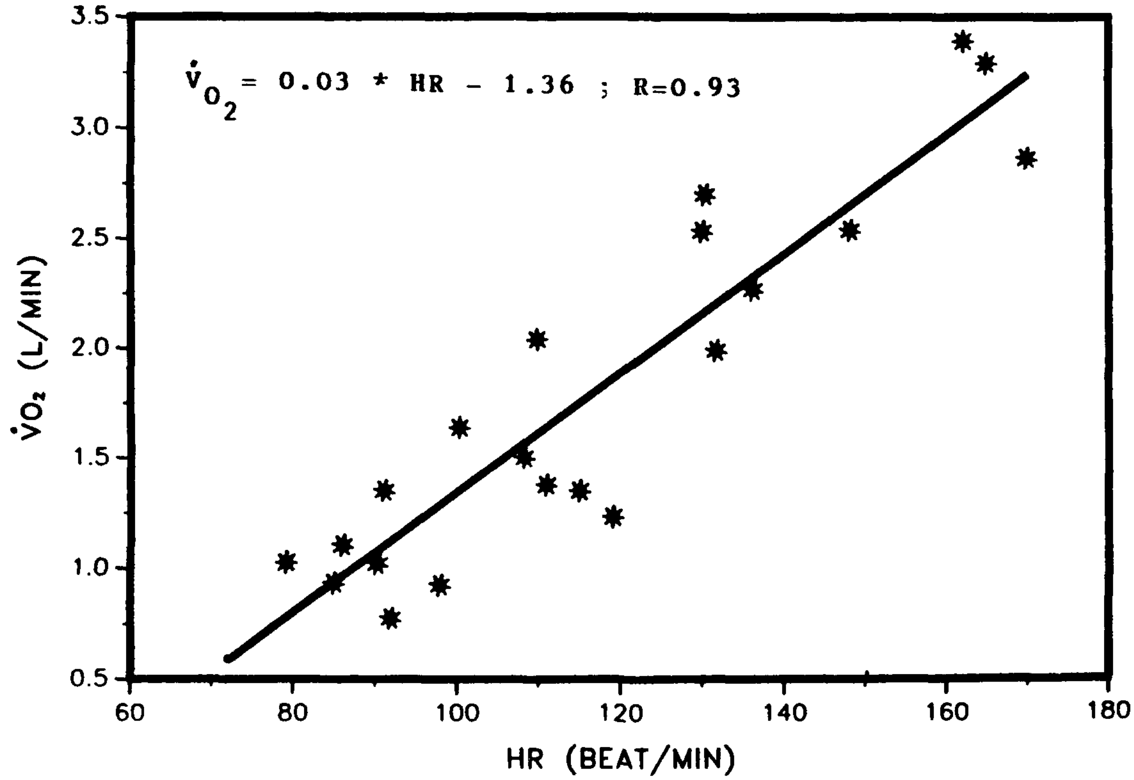

FIGURE 2 Oxygen uptake ($\dot{V}O_2$) - heart rate (HR) relationship obtained during cycling using the high flow rate analyzer (LB-2) and recirculation circuit and the low flow rate analyzer (mass spectrometer)

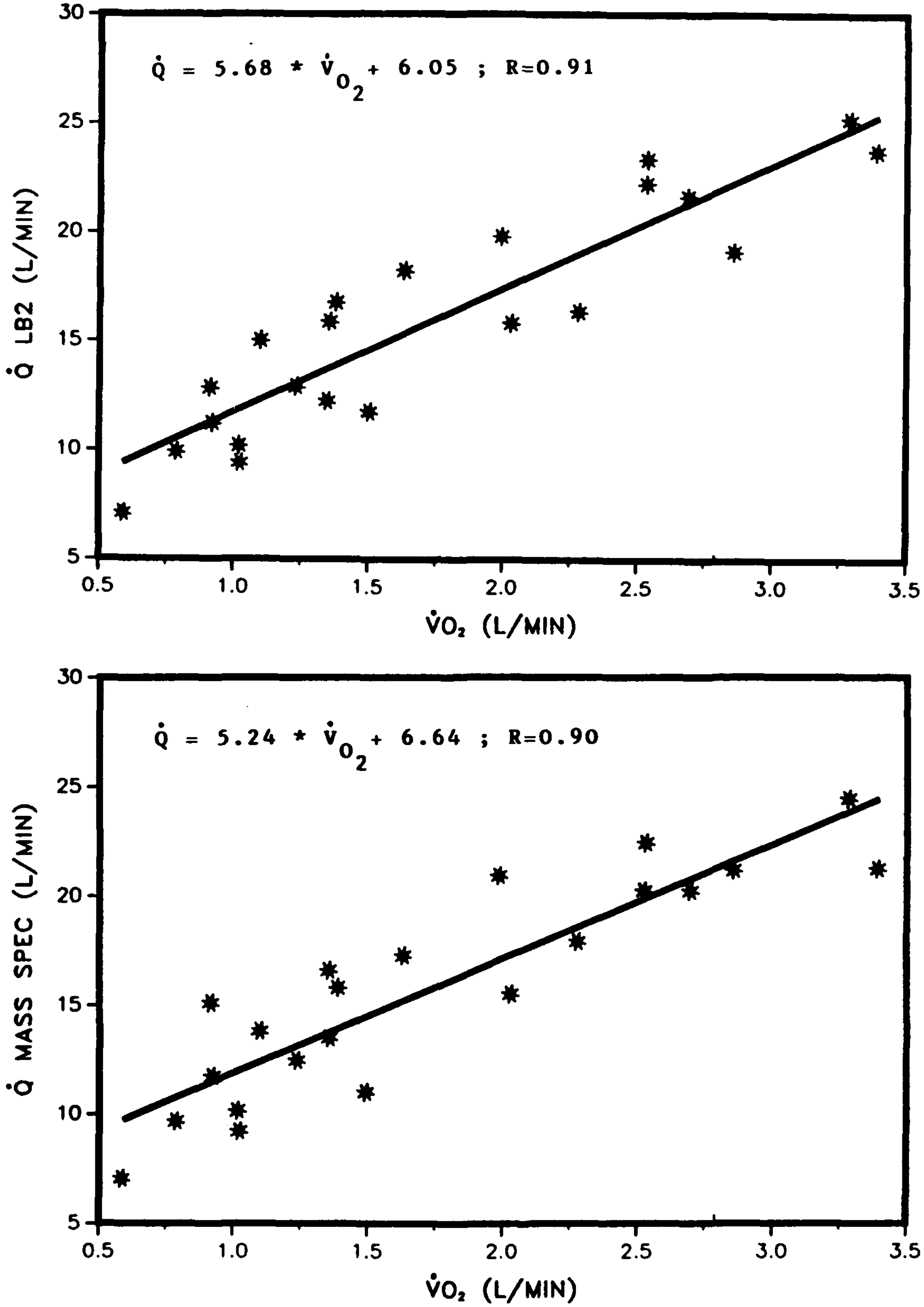

FIGURE 3 Cardiac output ($\dot{Q}$) - oxygen uptake ($\dot{V}O_2$) relationship measured during cycling using the LB-2 analyzer and recirculation circuit (TOP) and the mass spectrometer (BOTTOM)

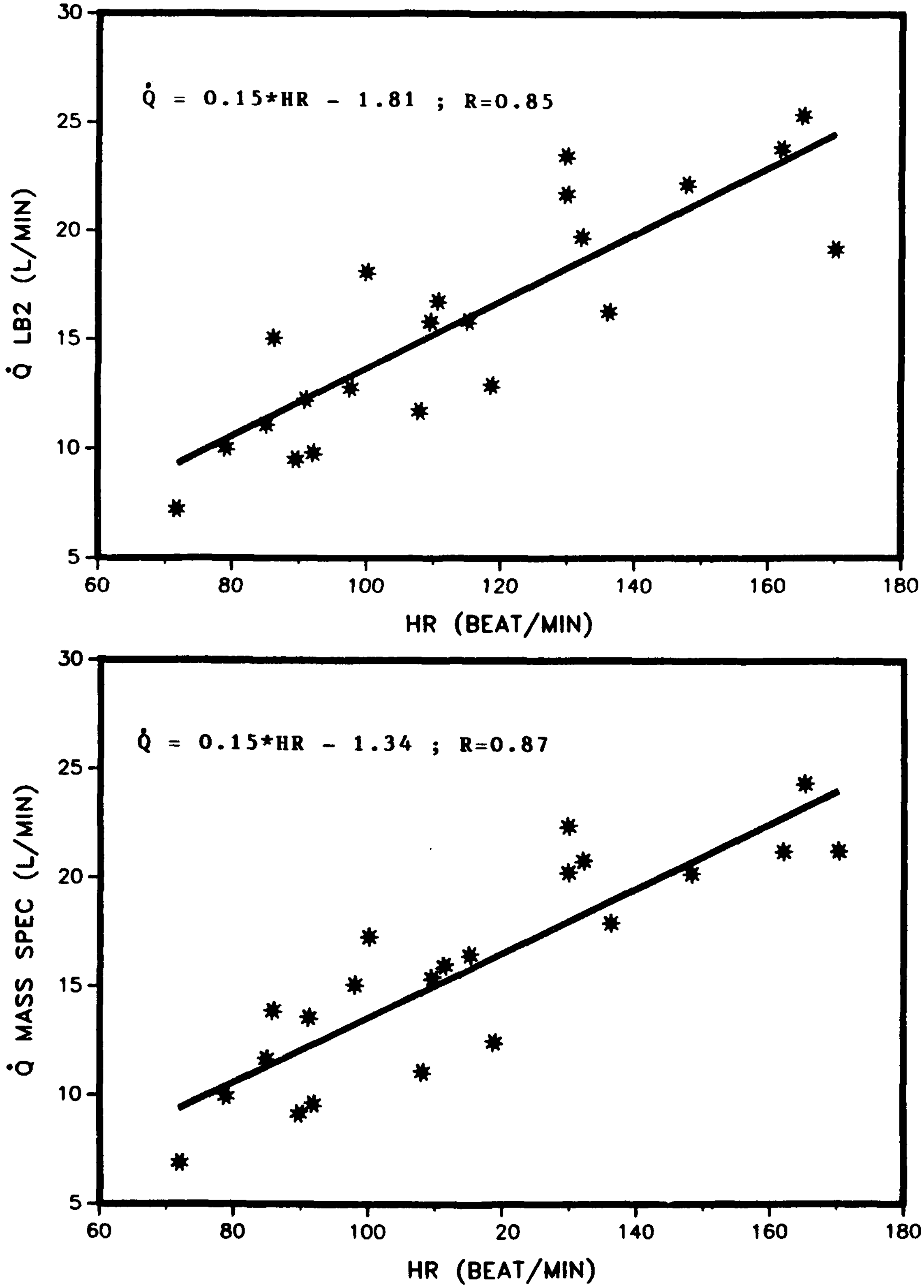

FIGURE 4 Cardiac output ($\dot{Q}$) - heart rate (HR) relationship obtained for exercise using the LB-2 CO_2 analyzer and recirculation circuit (TOP) and the mass spectrometer (BOTTOM)

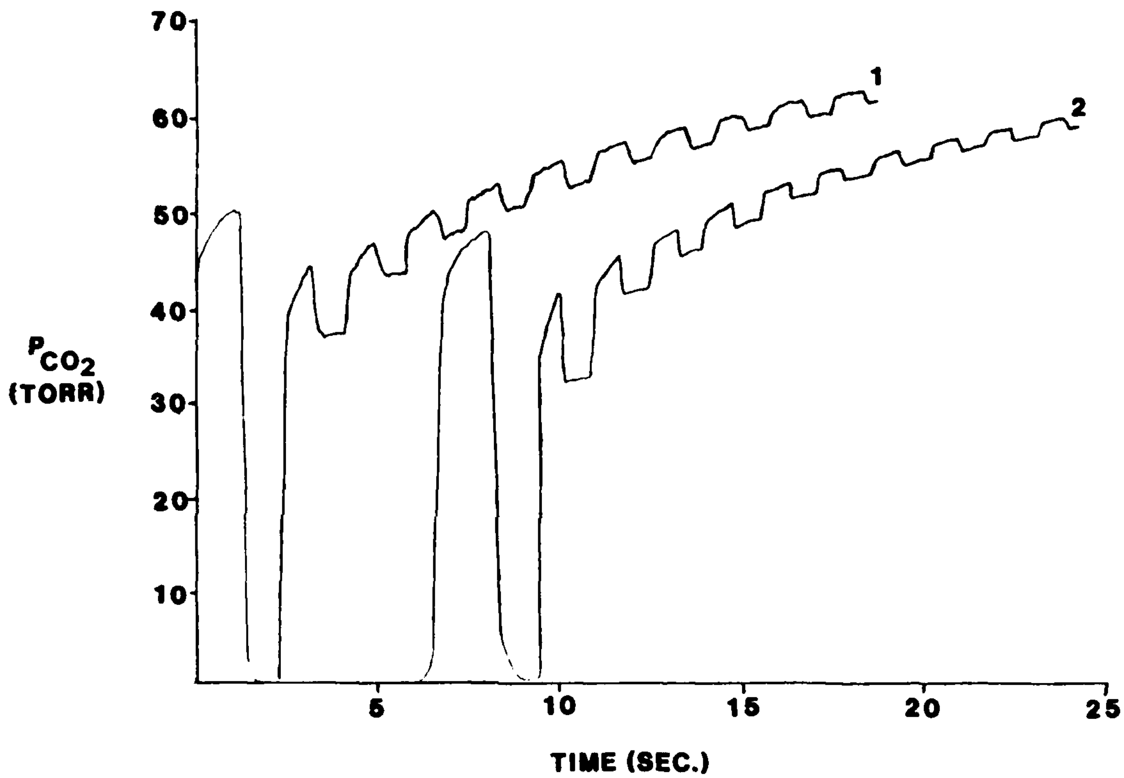

FIGURE 5 Experimental tracings depicting PCO_2 measured at the mouth during rebreathing using the high flow rate CO_2 analyzer (Beckman LB-2) and recirculation circuit (1) and the low flow rate gas analyzer (mass spectrometer) (2)

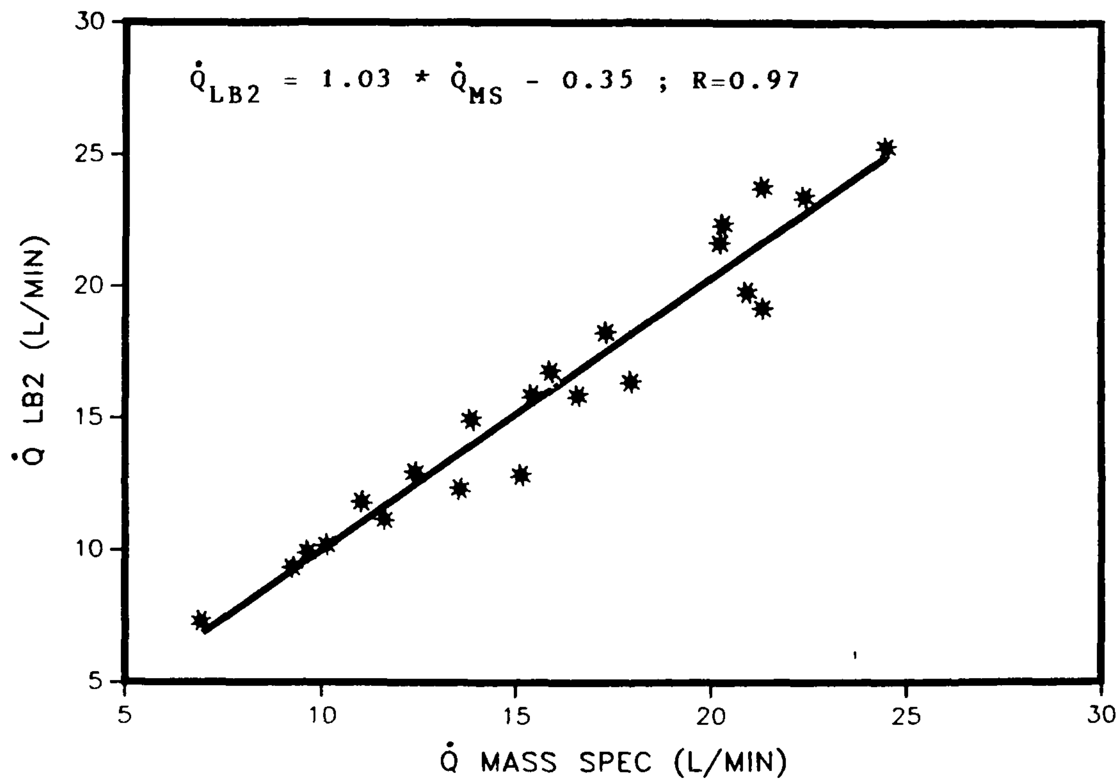

FIGURE 6 Comparison of cardiac output measured with low flow rate analyzer (LB-2) and recirculation circuit (ordinate) and with high flow rate analyzer (mass spectrometer) (abscissa)

TABLE 3

COMPARISON OF REBREATHING BAG VOLUME

TO TIDAL VOLUMES (V_T) MEASURED AFTER MANEUVER

Sub	$\%\dot{V}O_2max$	Rebreath[+] Bag Vol (L)	Range of V_T (L)	Average V_T (L) ($\pm$1SE)	Mode for V_T (L)	Cardiac output ($L*min^{-1}$)
1	rest	1.6				11.8
		1.7+				11.2
		1.8				11.4
	37	2.0	1.5-1.9	1.7 (0.1)	1.8	16.8
		2.2+	2.4-3.3	2.9 (0.1)	3.2	16.1
		2.4	2.5-3.0	2.8 (0.1)	2.9	17.6
	62	2.9	3.0-3.3	3.1 (0.05)	3.2	21.1
		3.1+	3.0-4.0	3.6 (0.1)	3.3	21.4
		3.3	3.0-3.2	3.3 (0.1)	3.2	19.9
4	rest	0.6				5.7
		0.7+				6.6
		0.8				7.2
	35	1.3	1.3-1.7	1.6 (0.04)	1.6	15.3
		1.5+	1.3-1.7	1.5 (0.05)	1.5	17.2
		1.7	1.3-1.7	1.5 (0.04)	1.5	15.9
	67	1.7	1.6-1.8	1.7 (0.02)	1.7	20.4
		1.9+	1.7-2.1	1.8 (0.03)	1.8	21.0
		2.1	1.7-2.2	1.9 (0.04)	2.0	21.6
5	rest	0.7				5.85
		0.8+				5.5
		0.9				7.1
	40	0.9	1.0-1.4	1.1 (0.04)	1.0	12.2
		1.1+	0.9-1.4	1.2 (0.05)	1.3	13.6
		1.3	0.9-1.1	1.0 (0.03)	1.1	12.2
	71	1.2	1.1-1.6	1.3 (0.03)	1.3	17.8
		1.4+	1.4-1.8	1.7 (0.05)	1.6	18.4
		1.6	1.3-1.8	1.5 (0.05)	1.3	16.1
6	rest	0.5				3.95
		0.6+				4.5
		0.7				@
	24	0.8	0.5-0.9	0.8 (0.03)	0.7	5.1
		1.0+	0.9-1.3	1.0 (0.03)	1.1	8.2
		1.2	0.9-1.1	1.0 (0.02)	1.0	7.9
	45	1.0	1.0-1.7	1.3 (0.04)	1.3	9.5
		1.2+	0.9-1.6	1.2 (0.05)	1.3	9.7
		1.4	0.9-1.4	1.1 (0.04)	1.1	9.2

Rebreathing bag volume denoted by + was equivalent to initial tidal volume (V_T) measure

@ cardiac output= 7.6 $L*min^{-1}$ but rebreathing frequency was 53 min-1

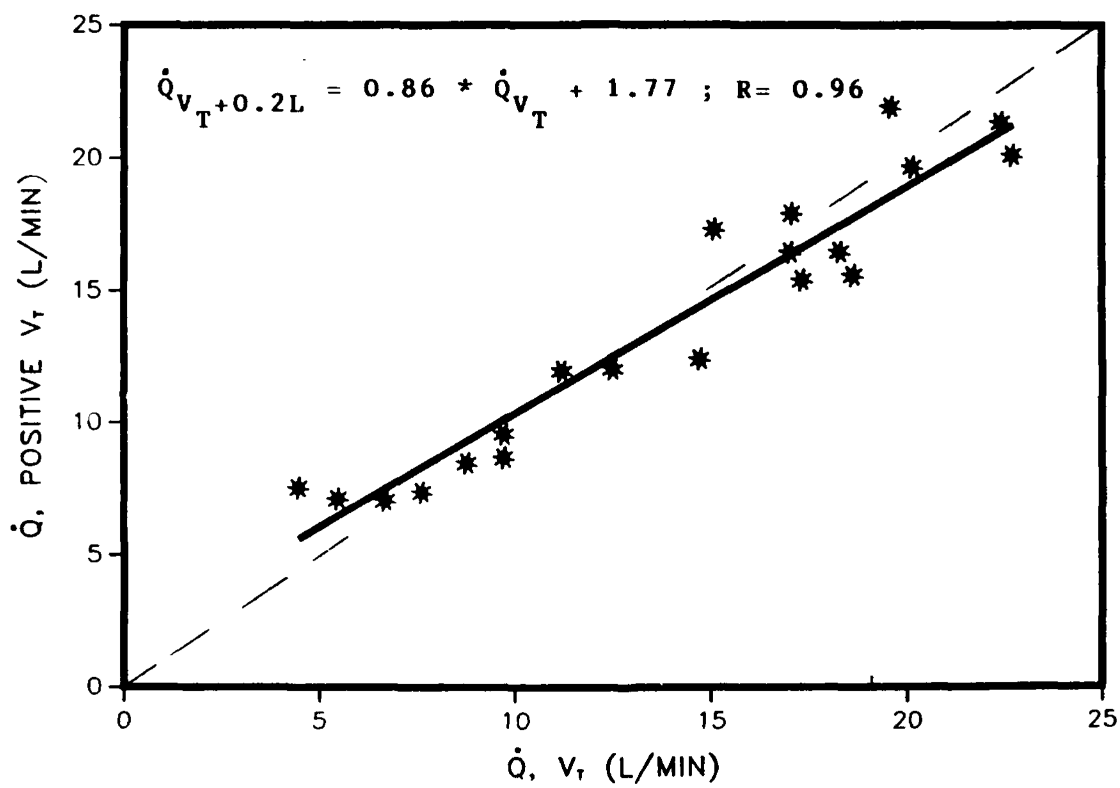

FIGURE 7 Comparison of estimates of cardiac output obtained with rebreathing bag volume equivalent to tidal volume (V_T)+ 0.2L (ordinate) and to V_T (abscissa) using LB-2 CO_2 and recirculation circuit

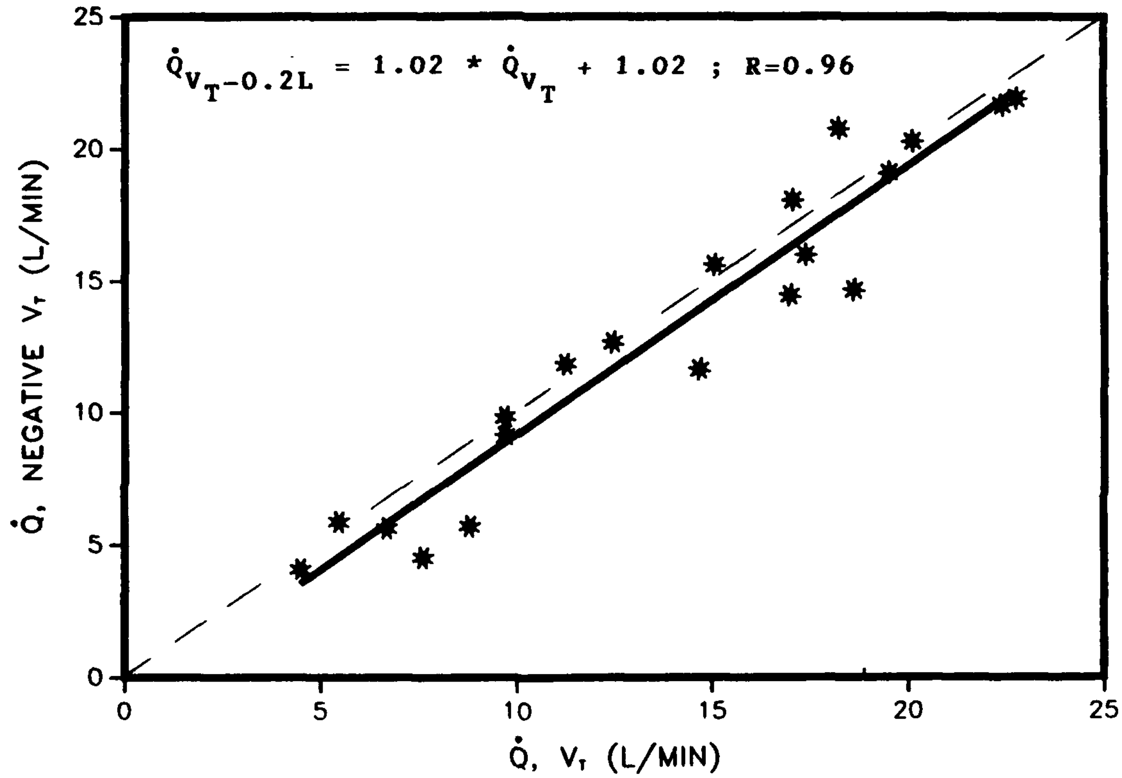

FIGURE 8 Comparison of cardiac output obtained with rebreathing bag volume equal to V_T- 0.2L (ordinate) and to V_T (abscissa) using the LB-2 analyzer and recirculation circuit

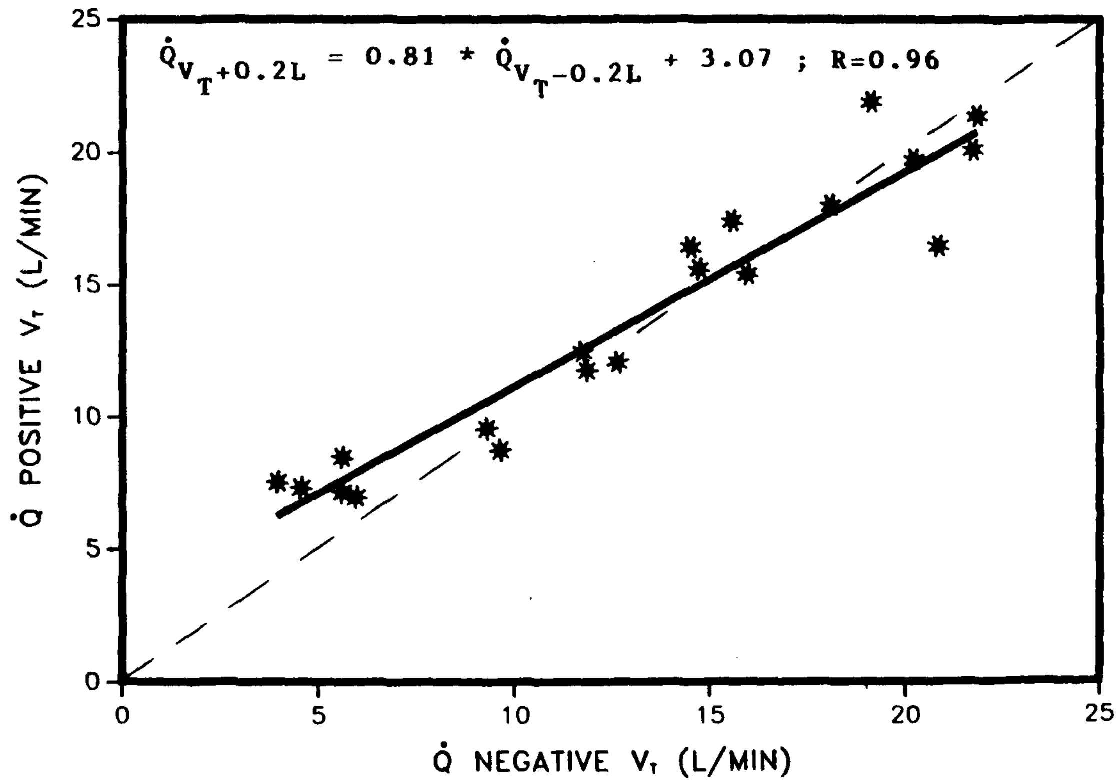

FIGURE 9 Comparison of cardiac output values obtained with rebreathing bag volume equal to V_T+ 0.2L (ordinate) and to V_T- 0.2L (abscissa) using our modified LB-2 CO_2 analyzer-recirculation system

respectively. Changing bag volume by $\pm$ 0.1L from rest V_T resulted in differences in cardiac output ranging from 0.2 $L*min^{-1}$ in subject 1 to 1.6 $L*min^{-1}$ in subject 5. No specific directional trend for estimates of cardiac output were observed when bag volume was reduced but increases in cardiac output of 0.2 $L*min^{-1}$, 0.6 $L*min^{-1}$, and 1.6 $L*min^{-1}$ for subjects 1, 4 and 5, respectively were noted when bag volume was increased by 0.1L.

TABLE 3 also shows the range of V_T, the average V_T, and the mode for V_T obtained during the $\dot{V}O_2$ collections. The initial measure of exercise V_T which was used for dispensing bag volume (denoted by the symbol +) was not significantly different from the range or mode for V_T obtained during subsequent $\dot{V}O_2$ collections. Although V_T varied breath to breath, the average and mode for V_T remained relatively unchanged over a 15-20 minute interval of data collection during submaximal cycling.

<u>Day 3. Effects of breath frequency during the rebreathing maneuver on the value of cardiac output obtained with our recirculation circuit</u>

TABLE 4 shows the values of cardiac output determined using different breathing frequencies during the rebreathing maneuver. Although we had few repetitive measures for only four (4) subjects at rest, the data indicates that the breathing frequencies recommended by Farhi (1) (25-35 min^{-1}) did not produce the most reproducible estimates for resting cardiac output. However, more variation in the value for resting cardiac output was noted when rebreathing frequencies of 46-55 min^{-1} were used.

DISCUSSION AND MILITARY RELEVANCE

The main objectives of this investigation were to modify the Farhi one-step rebreathing technique for measuring cardiac output and then validate our modification. Cardiac output and stroke volume in conjunction with heart rate

TABLE 4

EFFECT OF BREATHING FREQUENCY DURING THE REBREATHING MANEUVER

ON THE ESTIMATE OF CARDIAC OUTPUT*

	Cardiac output ($L*min^{-1}$) (f= 27-36 min^{-1})+				Cardiac output ($L*min^{-1}$) (f= 46-55 min^{-1})			
Subject	(n)	mean	min	max	(n)	mean	min	max
1	(6)	7.8	7.0	8.6	(2)	7.9	6.3	9.5
2	(4)	6.9	5.1	7.6	(2)	7.6	6.8	8.5
4	(4)	7.3	5.8	8.7	(7)	10.2	8.2	12.2
6	(4)	4.1	3.1	5.2	(5)	6.7	5.0	7.6

* cardiac output determined during rest using Beckman LB-2 analyzer and recirculation circuit

\+ frequency (f) was rebreathing frequency

and blood pressure define an individual's circulatory system. Because our research projects investigate circulatory function and fluid balance in heatstroke patients and in soldiers during military training exercises, we need a quick, reliable and noninvasive method to determine cardiac output in both laboratory and field settings. The rebreathing technique developed by Farhi and coworkers (1) effectively meets this requirement. The novelty of Farhi's technique is that it requires only one-step, takes less than 30 seconds for each maneuver, can be repeated at 1-2 minute intervals, and is accurate and reproducible. One drawback to the prescribed methodology and initially a major obstacle in our laboratory, was the requirement for a low flow rate (40- 60 $ml*min^{-1}$) CO_2 analyzer or mass spectrometer for sampling CO_2 at the mouth during rebreathing without compromising bag volume.

We modified Farhi's technique because 1) a low flow rate CO_2 analyzer was not available for our frequent use, 2) high purchase costs of low flow rate gas analyzer or metabolic cart were/are prohibitive, and 3) mass spectrometers and metabolic carts are not readily field portable due to their size and electrical requirements. We assembled a system incorporating equipment that was already present in the laboratory or could be purchased at a nominal cost. By substituting a high flow rate analyzer (Beckman LB-2 CO_2 analyzer) for the mass spectrometer, reducing the length of the sampling tubing on the LB-2 analyzer and then adding a recirculation circuit from the exhaust output of the analyzer to an inlet at the base of the rebreathing bag, we were able to recirculate the subject's expired gases and achieve no loss of bag volume.

Nearly simultaneous estimates of cardiac output were determined using two different instruments for CO_2 analysis: a low flow rate mass spectrometer and a high flow rate CO_2 analyzer with recirculation circuit. The relationship

for cardiac output generated from these two analyzers was described by a regression line close to identity (FIGURE 6). The excellent correlation ($R= 0.97$) of the data indicated that there was no statistically significant difference between the two methods of CO_2 analysis in estimating cardiac output.

The oxygen uptake ($\dot{V}O_2$) and cardiac output ($\dot{Q}$) relationship generated in the present study was linear and remarkably predictable during graded cycle exercise as previously demonstrated for both treadmill and cycle exercise (2, 5, 15). Faulkner and coworkers (2) have shown that the $\dot{Q}$-$\dot{V}O_2$ relationship measured with a slower multiple step rebreathing method and a high flow rate CO_2 analyzer, is described by the equation: $\dot{Q}= 5.2*\dot{V}O_2+ 5.2$. Using similar laborious methodology, this relationship has been described by regression lines of $\dot{Q}= 6.2* \dot{V}O_2+ 3.1$ (5) and $\dot{Q}= 4.96* \dot{V}O_2+ 5.12$ (3). In the present investigation, we computed *regression* lines of $\dot{Q}= 5.2* \dot{V}O_2+ 6.6$ and $\dot{Q}= 5.6* \dot{V}O_2+ 6.1$ for the mass spectrometer and LB-2 analyzer, respectively (see FIGURE 3). Because there was no statistical difference between the regressions for the two analyzer systems, we combined all data from "day 1" and "day 2" protocols and calculated a single regression having the form of $\dot{Q}= 5.5* \dot{V}O_2+ 5.75$, $R= 0.91$. Our data best agrees with that of Pendergast (personal communication, SUNY at Buffalo, NY) who used the Farhi technique and observed that $\dot{Q}= 5.65* \dot{V}O_2+ 5.0$ for a combination of exercise regiments and with Smyth and coworkers (15) who calculated for treadmill running, $\dot{Q}= 4.82* \dot{V}O_2+ 6.7$ using dye-dilution and $\dot{Q}= 5.04* \dot{V}O_2+ 4.67$ using acetylene rebreathing. Aside from Pendergast, we were unable to identify another group who generated the $\dot{Q}$-$\dot{V}O_2$ relationship for graded exercise using a one-step CO_2 rebreathing maneuver. In contrast to the rebreathing technique and computations for cardiac output used in the present study, these other studies

(2, 3, 5, 7, 8, 15) used the $\dot{V}O_2$ ($\dot{V}CO_2$) measure in calculating cardiac output. Thus, it is not surprising that good correlations between cardiac output and $\dot{V}O_2$ were found by these authors. The slope of the regression line in the present study agrees well with all of these studies. Several possible explanations for the slightly higher intercept observed by ourselves and Smyth et al. (15) are: 1) it is an inherent technical flaw, 2) the subject's initial breaths during the rebreathing maneuver were either too rapid or too slow, 3) the subject's last expired breath prior to rebreathing was beyond functional residual capacity, 4) the subject's ability and confidence in performing the maneuver would have benefited from additional practice, or 5) our subjects were above average fitness. Although a controversial subject, it has been suggested that physically fit and active young men have intercepts of 0.8- 2.2L greater than the norm for the $\dot{Q}$-$\dot{V}O_2$ relationship. The higher intercept in the present investigation is, most probably, a combination of several factors. The fact that the cardiac output values generated using the LB-2 CO_2 analyzer were not significantly different from the mass spectrometer data provides solid evidence that our estimates of cardiac output are valid.

Unlike other authors who did not meticuously monitor bag volume (2, 3, 7, 8, 15), Farhi emphasized the importance of the rebreathing bag volume being nearly equivalent to the subject's tidal volume. A unique feature of our method is that the subject's tidal volume was measured prior to the rebreathing maneuver, and that we used this measure to dispense the initial bag volume. Moreover, we verified tidal volume during all $\dot{V}O_2$ collections. Breath to breath variability in tidal volume was seen before, during and after all exercise rebreathing maneuvers in the present study (see TABLE 3). This agrees with what has been reported at rest (6) and during submaximal exercise (4). Although the maximum variation in breath to breath tidal volume measured

in a subject at a given work level was 0.9L, the usual breath to breath variation was about 0.4L or $\pm$ 0.2L. Of more importance was the finding that neither the mode nor the average tidal volume at each work load was significantly different from the initial measure of tidal volume which was subsequently used as the rebreathing bag volume.

Although no significant differences in our estimate of exercise cardiac output were noted when bag volume was altered by $\pm$ 0.2L, FIGURES 7-9 illustrate a slight deviation from identity. Comparison of estimates of exercise cardiac output in FIGURE 7 demonstrates that cardiac output obtained with bag volumes equal to V_T+ 0.2L was 1.1 L*min^{-1} greater than the line of identity at low output ($\dot{Q}$= 5 L*min^{-1}) and 1.0 L*min^{-1} less than the line of identity at high output ($\dot{Q}$= 20 L*min^{-1}). Additionally, when bag volume was reduced by 0.2L, estimates of exercise cardiac output were lower by 1.0 L*min^{-1} at all levels. Directional trends in exercise cardiac output were not observed when bag volumes were altered by 0.2L. These results suggest the possibility of variability in the estimation of cardiac output using bag volumes greater or less than the variation in tidal volume.

Compared to the exercise values, more variance in rest cardiac outputs was observed when bag volume was changed by 0.1L from the measured tidal volume. With the exception of one value from subject 6 ($\dot{Q}$= 7.6 L*min^{-1} when bag volume= V_T+ 0.1L and rebreathing frequency= 53 min^{-1}) which was excluded from TABLE 3, no other differences in cardiac output can be attributed to differences in rebreathing frequency. As noted for exercise, directional changes in rest cardiac output were not seen when bag volume was altered.

Several factors likely to share responsibility for the variation in measures of rest cardiac output are: 1) subjects were not in a true restful state, but rather in a "pre-exercise" state in anticipation of cycling, 2)

positional changes while seated on the cycle affected lung volumes and/or heart rate, 3) subjects were holding their breath at the end of expiration while leisurely turning the stopcock, and 4) overestimation of the approximation of equilibrium of the CO_2 dissociation curve occurred (1). Overall, we suspect that both positional changes and absence of a "true" rest state while subjects sat on the cycle contributed to the observed variation in rest cardiac output.

Another factor which Farhi and coworkers (1) found critical for the determination of cardiac output is the subject's breathing frequency during the rebreathing maneuver. We followed the recommendations of Farhi and associates (1) by choosing a rebreathing frequency and bag volume such that the alveolar PCO_2 would initially drop and then rise to pre-rebreathing levels in less than 10 seconds. Farhi and coworkers (1) used rebreathing frequencies of 25-30 min^{-1} during rest and 30-35 min^{-1} during exercise. In the present study, using rebreathing frequencies of 27-36 min^{-1} in the "resting" subject did not result in highly consistent estimates for cardiac output in three of four subjects studied (TABLE 4). Moreover, even greater variability in rest values of cardiac output was obtained with high breathing frequencies ($f = 46-55\ min^{-1}$). No consistent trend in resting cardiac output with increased rebreathing frequencies was seen. Again, we suspect that part of this intermeasure variability resulted from differing levels of restfulness.

Rebreathing frequencies ranging from 20 min^{-1} to 50 min^{-1} have been used in obtaining rest and exercise estimates of cardiac output with the multiple step CO_2 rebreathing technique (2, 3, 7, 8). That using too low or too high a breathing frequency can produce inaccurate estimates was shown by Jernerus and coworkers (7). These authors recommend using frequencies of about 30 min^{-1} at

rest and 50 min^{-1} during work. Compared to both dye-dilution and direct Fick, high rebreathing frequencies resulted in lower values of cardiac output during rest and higher values during exercise (7). According to Farhi and associates (1), rebreathing frequencies less than 25 min^{-1} do not produce the initial fall in alveolar PCO_2, are difficult to analyze and provide unusable results. We would expect that breathing at frequencies greater than 46 min^{-1} during rest would cause CO_2 to be expired out of proportion to the low metabolic rate and an equilibrium PCO_2 to be prematurely reached, thereby producing erroneously high estimates of rest or pre-exercise cardiac output.

Rebreathing frequencies were calculated for the duplicate runs at each bag volume for each subject in TABLE 3. The average frequency used by the four subjects during the rebreathing maneuver while cycling at 24-71 $\%\dot{V}O_2max$ was $42 \pm 3 \pm 2$ min^{-1} ($\pm$ SD$\pm$ SE). Individual frequencies averaged $40 \pm 3 \pm 1$ min^{-1}, $38 \pm 3 \pm 1$ min^{-1}, $45 \pm 4 \pm 1$ min^{-1}, and $45 \pm 7 \pm 2$ min^{-1} for subjects 1, 4, 5, and 6 respectively. When assessing Farhi's method during recumbent exercise, Ohlsson and Wranne (10) used an average rebreathing frequency of 35 min^{-1} and found good correlation in the cardiac output values obtained with Farhi's and the direct Fick method. These authors did not provide actual or average frequencies with standard deviations. The typical range of rebreathing frequencies used during exercise in several studies was 35-50 min^{-1} (1, 2, 3, 7, 8, 9, 10, 15).

The good reproducibility of this technique as performed in our laboratory with our modifications is shown in TABLE 5. Rest or pre-exercise values for five subjects are shown for Trial 1, 2, 3 (V_T used as bag volume, TABLE 3) and 4 (mean value with rebreathing frequencies of 27-36 min^{-1}, TABLE 4). Although these measures were obtained on nonconsecutive days, excellent reproducibility of estimates for resting cardiac output was obtained. Differences between

TABLE 5

RESULTS OF MEASUREMENT OF CARDIAC OUTPUT*

ON NONCONSECUTIVE DAYS

Subject	Work load ($\%\dot{V}O_2max$)	Cardiac output ($L*min^{-1}$) trial 1	2	3	4	mean $\pm$ SD $\pm$ SE
1	rest	11.0	12.6	11.2	7.8	10.7 $\pm$ 2.0 $\pm$ 1.0
2	rest	6.5	6.0	---	6.9	6.5 $\pm$ 0.45 $\pm$ 0.3
4	rest	7.4	7.5	6.6	7.4	7.2 $\pm$ 0.4 $\pm$ 0.2
	29	---	---	15.4	15.8	
	37	---	16.8	17.2	---	
	54	21.1	22.3	---	21.7	
5	rest	5.4	5.6	5.5	---	5.5 $\pm$ 0.1 $\pm$ 0.05
6	rest	3.5	4.1	4.5	4.05	4.0 $\pm$ 0.3 $\pm$ 0.2
	25	---	7.3	8.2	7.2	
	33	---	9.3	---	9.0	
	50	---	12.9	---	12.0	

* Cardiac output measured with the LB-2 CO_2 analyzer and recirculation circuit

rest values ranged from 0.2 L*min^{-1} (subject 5) to an extreme of 4.8 L*min^{-1} (subject 1) and with the exception of one spurious value from subject 1, the standard deviations were remarkably small. Estimates of submaximal exercise cardiac output were obtained from subjects 4 and 6 on additional days and are compared to TABLE 2 and 3 values in TABLE 5. Similar to rest, exercise cardiac outputs measured on separate occasions displayed an excellent reproducibility with differences ranging from 0.1 L*min^{-1} to 1.3 L*min^{-1}.

Because of the strong agreement between cardiac output values determined using the LB-2 CO_2 analyzer with recirculation circuit and the low flow rate mass spectrometer, and the excellent agreement with the cardiac output values obtained in rest and exercise on nonconsecutive days and with those reported in the literature (exemplified by the $\dot{Q}$-$\dot{V}O_2$ relationship), we conclude that our modification of the Farhi technique is a valid means of determining cardiac output at rest and at submaximal worklevels. We recommend that subjects be in true rest states for rest values, that a minumum of 2 repetitive measures be gotten to insure reproducibility and that subjects attend several practice trials the prior to data collection. Thus, we can now quickly and reliably determine cardiac output in soldiers resting or working under a variety of environmental conditions in both the laboratory and field settings.

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Human subjects participated in this study after giving their informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on use of volunteers in research.

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